Endothelial Shear Stress and Coronary Plaque Characteristics in Humans
Combined Frequency-Domain Optical Coherence Tomography and Computational Fluid Dynamics Study

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Background—Despite the exposure of the entire vasculature to the atherogenic effects of systemic risk factors, atherosclerotic plaques preferentially develop at sites with disturbed flow. This study aimed at exploring in vivo the relationship between local endothelial shear stress (ESS) and coronary plaque characteristics in humans using computational fluid dynamics and frequency-domain optical coherence tomography.

Methods and Results—Three-dimensional coronary artery reconstruction was performed in 21 patients (24 arteries) presenting with acute coronary syndrome using frequency-domain optical coherence tomography and coronary angiography. Each coronary artery was divided into sequential 3-mm segments and analyzed for the assessment of local ESS and plaque characteristics. A total of 146 nonculprit segments were evaluated. Compared with segments with higher ESS [≥1 Pascal (Pa)], those with low ESS (<1 Pa) showed higher prevalence of lipid-rich plaques (37.5% versus 20.0%; \( P=0.019 \)) and thin-cap fibroatheroma (12.5% versus 2.0%; \( P=0.037 \)). Overall, lipid plaques in segments with low ESS had thinner fibrous cap (115 μm [63–166] versus 170 μm [107–219]; \( P=0.004 \)) and higher macrophage density (normalized standard deviation: 8.4% [4.8–12.6] versus 6.2% [4.2–8.8]; \( P=0.017 \)). Segments with low ESS showed more superficial calcifications (minimum calcification depth: 93 μm [50–140] versus 152 μm [105–258]; \( P=0.049 \)) and tended to have higher prevalence of spotty calcifications (26.0% versus 12.0%; \( P=0.076 \)).

Conclusions—Coronary regions exposed to low ESS are associated with larger lipid burden, thinner fibrous cap, and higher prevalence of thin-cap fibroatheroma in humans. Frequency-domain optical coherence tomography–based assessment of ESS and wall characteristics may be useful in identifying vulnerable coronary regions.

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Key Words: atherosclerosis ■ optical coherence tomography ■ shear stress

Despite the exposure of the entire vasculature to the atherogenic effects of systemic risk factors, atherosclerotic plaques develop at specific regions of the arterial tree where disturbed and low flow occurs and progress focally and eccentrically in an independent manner.\(^1\),\(^2\) Endothelial shear stress (ESS), the tangential stress generated by the friction of the flowing blood on the endothelial surface of the vessel wall, regulates much of endothelial function, and low ESS (<1.0 Pascal (Pa)) activates a myriad of intracellular pathways, leading to endothelial dysfunction, lipoprotein accumulation, and inflammation.\(^3\) Autopsy studies and animal models have demonstrated that atherosclerotic lesions with vulnerable features preferentially develop in areas with low ESS, such as the inner curvature of coronary arteries, the outer waist of a coronary bifurcation, and downstream from a luminal obstruction.\(^4\),\(^6\) In contrast, normal ESS (≈1–2.5 Pa), occurring...
in arterial segments that are straight and have no obstruction, is typically vasculoprotective, whereas high ESS (≥2.5 Pa), occurring at the throat of an obstruction or at the outer curvature of an artery, may be associated with local erosion and enhanced platelet aggregation.4–6

Recently, the Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology (PREDICTION) study showed in vivo the effect of low ESS on plaque progression by means of a systematic vascular profiling, which combined ESS computation with intravascular ultrasound (IVUS)–derived morphometric data.1 Interestingly, virtual histology-IVUS studies suggested an association between low ESS and plaque necrotic core and calcium areas.7 However, because of the lack of imaging modalities with adequate resolution, the in vivo relationship between local ESS and microscopic coronary plaque characteristics has never been investigated in humans.

Optical coherence tomography (OCT) is a high-resolution intracoronary imaging modality enabling an accurate in vivo characterization of atherosclerotic plaques.8 OCT is able to detect microstructural features, such as fibrous cap thickness, neovascularization, and macrophage density, and represents the modality of choice for the identification of thin-cap fibroatheroma (TCFA), considered the prototype of the ruptured-prone plaque.9

The aim of this study was to investigate in vivo the relationship between local ESS and coronary plaque features, using systematic vascular profiling, which combines computational fluid dynamics and frequency-domain (FD)-OCT analysis in humans.

Methods

Study Population
Patients with acute coronary syndrome (ACS) who underwent FD-OCT imaging before percutaneous coronary intervention were identified from the Massachusetts General Hospital OCT Registry database. Inclusion criteria were (1) FD-OCT pullback length ≥22 mm between corresponding proximal and distal anatomic landmarks (ie, major branches) to be used for three-dimensional (3D) reconstruction; (2) X-ray coronary angiograms with ≥2 projections with a difference in angle ≥35°; and (3) no history of previous stent implantation in the artery to be studied. From a total of 117 patients with ACS and pre-percutaneous coronary intervention FD-OCT, 29 patients were excluded because of an insufficient OCT segment length between 2 major branches, 14 patients because of inadequate coronary angiogram projections for 3D reconstruction, and 31 patients because of the presence of previously implanted stent in the artery to be studied. Finally, 19 patients were excluded because of an insufficient image quality of the OCT pullback and 3 patients because of incomplete demographic/clinical data. Therefore, data from a total of 21 patients (24 coronary arteries) were suitable for a combined computational fluid dynamics and OCT plaque analysis and were included in the study. The Massachusetts General Hospital OCT Registry was approved by each institutional review board, and all patients provided informed consent before enrollment.

Data Acquisition
Coronary angiograms were recorded with full contrast injection before the insertion of a guidewire and the OCT catheter. OCT pullback was performed after intracoronary administration of 100 to 200 μg nitroglycerin, using an FD-OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN). Automated pullback was initiated at a speed of 20 mm/sec (22 arteries) or 25 mm/sec (2 arteries) in concordance with blood clearance. All of the images were deidentified, digitally stored, and submitted to the Massachusetts General Hospital OCT Registry Laboratory for analysis. After proper Z-offset calibration, FD-OCT images were transferred in DICOM format to Vascular Profiling Laboratory at Brigham & Women’s Hospital for ESS computation.

Computational Fluid Dynamics and ESS Analysis

Image Analysis
3D coronary artery reconstruction was performed using FD-OCT and coronary angiograms. Two end-diastolic images were selected by the angiographic projections that portrayed the most distal and proximal anatomic landmark detected also in the FD-OCT images. The portion of the artery defined from the distal and proximal anatomic landmark was reconstructed using the FD-OCT data. FD-OCT image sequences were reviewed to identify the most common distal and proximal fiducial markers (ie, side branches) that were visible in both FD-OCT and coronary angiograms.

3D Coronary Artery Reconstruction
The reconstruction methodology used the 3D luminal centerline derived from the angiographic projections as a backbone to reconstruct the coronary artery, thereby incorporating the 3D curved course of the artery with any local curvature on the epicardial surface into the 3D coronary model.10 The borders of the lumen were detected in the FD-OCT images. Because of the high speed (20–25 mm/sec) of the FD-OCT pullback, which only includes 2 to 3 cardiac cycles, and because of the continuous FD-OCT catheter translocation within the lumen, the use of images from various phases of the cardiac cycle at fixed intervals (eg, 0.2 mm) was necessary for lumen segmentation. The selected end-diastolic angiograms were processed for edge detection of the lumen borders and then estimation of the luminal centerline.10 The 2 centerlines assessed in the angiograms were used to define 2 B-splines which were extruded normal to their plane, each one forming a surface.10 The interaction of the 2 surfaces was a 3D curve, which corresponded to the 3D luminal centerline. The center of mass (ie, centroid) of the lumen area from the FD-OCT images was determined, and the OCT-derived lumen borders were placed perpendicularly onto the 3D lumen centerline in equidistant locations, positioning the lumen centroids on the 3D centerline. The relative rotational orientation of the FD-OCT frames was estimated using 3D geometry algorithms, whereas the absolute rotational orientation of the first FD-OCT frame was estimated using the orientation of side branches. The lumen 3D boundary points derived from the abovementioned methodology were connected to build the FD-OCT–based lumen geometry in 3D space.

Blood Flow Simulation and ESS Computation
The obtained 3D coronary reconstructions were further processed with computational fluid dynamics techniques, which can provide detailed characteristics of intravascular blood flow and local ESS distribution. These techniques involve the generation of a finite volume mesh to perform blood flow simulation by solving the 3D transport equations governing the conservation of mass and momentum (ICEM CFD and CFX 11, Ansys, Canonsburg, PA).11 Coronary blood flow for the reconstructed arterial segment was calculated directly from the time required for the volume of blood contained within the segment to be displaced by radio-opaque material during a contrast injection. The true 3D volume of the segment was first computed from the 3D lumen reconstruction. The number of cine-frames required for the contrast medium to pass from the inlet to the outlet of the studied segment was calculated. The flow rate (mL/s) was calculated as (frame rate [frames/sec] × volume [mL]) / frame count.12 Blood rheological behavior was approximated by a homogeneous and Newtonian fluid with a dynamic viscosity of 0.0035 Pa·s and a density of 1050 kg/m³.11–13 Blood flow was considered to be laminar and incompressible, and the no-slip condition assuming rigid walls was applied. ESS at the endothelial surface of the artery was calculated as the product of blood viscosity and the gradient of blood velocity at the wall. The entire reconstructed artery was divided into consecutive 3-mm segments starting at the inlet, and each 3-mm segment was characterized by local predominant ESS value (defined as the minimum averaged ESS value over a 90° arc in each 3-mm segment).1 To minimize the effect of established and developing stenoses when assessing the
preceding (ie, baseline) local hemodynamic behavior and to explore the relationship between baseline local ESS and coronary plaque features using OCT data at a single time point, segments with significant stenosis (>40% area stenosis) were excluded. Therefore, only non-culprit segments without significant stenosis were considered in the analysis. We chose 3-mm segments since this length has been shown to accurately reflect the local hemodynamic and vascular characteristics in previous studies investigating the in vivo role of ESS in the pathophysiology of coronary artery disease. According to the magnitude of local ESS, coronary segments were divided into segments with low ESS (<1 Pa) and those with higher ESS (≥1 Pa; Figure 1).

OCT Image Analysis

FD-OCT images in each 3-mm segment obtained from the 3D reconstructed models were analyzed every single frame (0.2 mm) by 2 independent investigators who were blinded to clinical, laboratory, and vascular profiling data. When there was discordance between the observers, a consensus was obtained. Offline analysis was performed using proprietary software (LightLab Imaging) after confirming proper calibration settings of the Z-offset. Lipid plaque was defined as a diffusely bordered signal-poor region with an overlying signal-rich band, and lipid arc was measured every 1 mm.8,14 We defined lipid-rich plaque as a lesion in which the lipid arc subtended an angle ≥90°.8,14 Fibrous cap thickness of a lipid plaque was measured 3 times at its thinnest part, and the averaged value was used.14 TCFA was defined as lipid-rich plaque covered by a fibrous cap thinner than 65 μm.8,14,15 For the assessment of macrophage density, each fibrous cap was automatically segmented using a previously validated algorithm,16 and the normalized standard deviation (NSD) of the OCT signal-poor vesicular or tubular structures (microchannels) with a diameter of 50 to 300 μm.14 The minimum distance from the microchannels to the luminal surface was recorded.

Statistical Analysis

Categorical variables are presented as counts and percentages; continuous variables are expressed as mean±SD or median and inter-quartile range (IQR) as appropriate. For the comparison of plaque characteristics between the 2 groups, the generalized estimating equations approach was used to take into account the within-subject

<table>
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<th>Table. Baseline Demographic and Clinical Characteristics</th>
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<td>ACE-inhibitors, n (%)</td>
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Continuous variables are presented as median (interquartile range). Patients are on multiple medications; therefore, the total is larger than 21.

ACE-i indicates angiotensin converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; and STEMI, ST-segment elevation myocardial infarction.
correlation because of the analysis of multiple segments in a single patient. All tests were 2-tailed, and an α-level of 0.05 was used to determine statistical significance. All statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL).

Results

A total of 146 3-mm segments from 24 coronary epicardial vessels in 21 patients were analyzed. Baseline demographic and clinical characteristics are summarized in the Table. The majority of patients had substantial coronary risk factors and presented with non-ST-elevation myocardial infarction or unstable angina. Fasting lipids were modestly elevated and cardiovascular risk, as measured by C-reactive protein, was low. At presentation, about one fourth of patients were on antiplatelet therapy and more than one third on statin therapy. Vascular profiling and analysis of plaque characteristics were performed successfully in all studied coronary arteries, which included 8 left anterior descending arteries, 10 right coronary arteries, and 6 left circumflex arteries. The median ESS value was 0.74 Pa (IQR, 0.44–1.23). A total of 96 (65.7%) segments were characterized by low local ESS and 50 (34.3%) segments by higher local ESS.

Regions with low ESS had higher prevalence of lipid-rich plaques (37.5% versus 20.0%; P=0.019), thinner fibrous cap (115 μm [IQR, 63–166] versus 170 μm [IQR, 107–219]; P=0.004), and higher prevalence of TCFA (12.5% versus 2.0%; P=0.037) compared with those with higher ESS (Figure 2). Furthermore, compared with segments with higher ESS, those with low ESS showed a greater number of cross-sections with lipid plaque (4.8±6.1 versus 2.8±4.5; P=0.021) and a greater lipid arc (101° [IQR, 85–123] versus 85° [IQR, 71–95]; P=0.025). Macrophage density within the fibrous cap, expressed as NSD of the raw OCT signal, was significantly higher in segments with low ESS than in those with higher ESS (8.4% [IQR, 4.8–12.6] versus 6.2% [IQR, 4.2–8.8]; P=0.017; Figure 3).

The prevalence of coronary calcifications was not significantly different between segments with low ESS and those with higher ESS (37.5% versus 24.0%, P=0.242; Figure 4A). Segments with low ESS tended to have higher prevalence of spotty calcifications compared with those with higher ESS (26.0% versus 12.0%, P=0.076; Figure 4B). Coronary calcifications were more superficially located in segments with low ESS than in those with higher ESS (minimum calcification depth: 93 μm [IQR, 50–140] versus 152 μm [IQR, 105–258]; P=0.049; Figure 4C).

The prevalence of neovascularization was not significantly different between segments with low and those with higher ESS (16.7% versus 34.0%, P=0.170), as well as the minimum neovascularization depth (229 μm [IQR, 148–414] versus 247 μm [IQR, 184–334]; P=0.990).

Discussion

This study represents the first in vivo evaluation of the relationship between local ESS and OCT-derived coronary plaque characteristics in humans. We used the high spatial resolution of FD-OCT to study the detailed pathobiological plaque characteristics in relation to the local ESS pattern. Areas with low local ESS were more frequently associated with the presence of lipid-rich plaques and TCFA. Overall, plaques in areas with low ESS showed larger lipid accumulation, thinner fibrous cap, and higher OCT-derived macrophage density. Segments with low ESS had more superficial calcifications and tended to have higher prevalence of spotty calcifications.

We observed in vivo that coronary areas exposed to low ESS were associated with a significantly higher prevalence of TCFA, which is considered to be the prototype of the rupture-prone plaque. Pathology studies identify TCFA, a plaque composed of a large necrotic core covered by a thin (<65 μm) fibrous cap, as the typical underlying morphology of plaque rupture, which represents the cause of two thirds of ACS.20 The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, using deductive inferences based on radio-frequency signal deconstruction and virtual histology-IVUS showed that TCFA was the highest-risk plaque phenotype associated with 3-year major adverse cardiovascular events.21 However, the in vivo IVUS imaging was insensitive to the detailed characteristics of histological TCFA. Using high resolution FD-OCT imaging, we were able to accurately characterize coronary plaques in vivo and to prove in humans the previous histological observations in diabetic, hypercholesterolemic pigs22 that TCFA are located preferentially in regions exposed to low ESS.

We found a higher prevalence of lipid-rich plaques in the segments exposed to low ESS, and these plaques were characterized by significantly larger lipid arc as compared with the segments with higher ESS. The role of low ESS in lipid accumulation is in part mediated by endothelial activation of sterol regulatory elements–binding proteins,23 a family of transcription factors which upregulates a series of genes encoding for cholesterol synthase, fatty acid synthase, and LDL receptor. This active sterol regulatory elements–binding proteins–dependent cholesterol synthesis and uptake promotes LDL subendothelial accumulation in the growing plaque, exacerbated by local flow stagnation and increased endothelial permeability.23
Although we found that TCFA localized almost exclusively in areas with low ESS, the majority of segments with low ESS in our study did not exhibit this plaque phenotype (ie, high sensitivity with low specificity). Therefore, although low ESS represents an important factor for the development of rupture-prone plaques, other systemic (eg, hypercholesterolemia, inflammation, oxidative stress, genetic predisposition) or local (eg, tensile stress) factors likely contribute to the development of these lesions. Furthermore, we speculate that regions with low ESS and high lipidic burden, which did not fulfill the criteria of TCFA at the time of study, are at high risk of developing into TCFA at a later time point, thereby indicating the overall ESS effect on the development of vulnerable plaques at different stages of the disease. Our observation of a high sensitivity but low specificity of low ESS for the identification of areas with TCFA indicates that the most appropriate strategy for a powerful prediction of future culprit lesions might be a multiple assessment of the vascular environment (ie, multimodality imaging of plaque morphology, ESS distribution, plaque activity) and the systemic risk profile.

Another critical finding of our study was the observation that lipid plaques exposed to low ESS were covered by a significantly thinner fibrous cap. Because of the high resolution of FD-OCT,9 we were able to correlate in vivo the local ESS pattern with these microscopic features of coronary plaques, which had not been previously feasible with other imaging modalities. The thinning of the fibrous cap in regions with low ESS can be explained by both a reduction in the synthesis of extracellular matrix, through interferon-γ–mediated inhibition of vascular smooth muscle cells and Fas-related vascular smooth muscle cell apoptosis, and an active degradation of extracellular matrix by proteases.3 In particular, low ESS has been shown to induce gene expression and activity of matrix metalloproteinases-2 and -9, and cathepsins in animal experiments.6,22

We also measured macrophage density within the fibrous cap by computational measurement of NSD of the OCT signal. This method has been validated by immunohistochemistry, demonstrating a high degree of positive correlation between OCT and histological measurements of macrophage density using CD68 staining (r=0.84, P<0.0001). Values of NSD >6.35% were previously able to discriminate fibrous caps with large macrophage density (CD68 staining >10% of the total cap area) with high sensitivity and specificity.17 In our study, in vivo FD-OCT imaging showed that segments with low ESS have higher NSD, reflecting a greater macrophage density. Low ESS is known to upregulate several genes encoding for adhesion molecules and chemokines, which may facilitate monocyte infiltration and differentiation to macrophages.3 This may translate into a higher predisposition to rupture of those lipid-rich plaques and TCFA located in areas with low ESS, as macrophage infiltration is an important determinant of plaque vulnerability, and previous studies indicated an association between macrophage infiltration in >10% of the total plaque area and a presentation with...
gressions, and recent OCT studies showed a positive correlation between focal superficial calcifications and more extensive and accelerated disease progression. Several studies suggest a role for superficial microcalcifications in increasing the mechanical stress on thin fibrous caps. Furthermore, we found that the presence of spotty calcifications tended to be more frequent in areas with low ESS. Spotty calcific deposits have been associated with more extensive and diffused coronary atherosclerosis and accelerated disease progression, and a recent OCT study showed a positive correlation between the number of spotty calcium deposits and plaque rupture. However, the role of superficial and spotty calcifications in coronary plaque vulnerability is not well defined, and our results need to be considered as hypothesis generating.

Limitations
The present study is limited by the small number of patients included in the analysis. However, this represents the first systematic in vivo human study investigating the relationship between local ESS and microscopic plaque characteristics assessed by FD-OCT. Second, most patients underwent OCT imaging of a single coronary artery; thus, the results were derived from a limited part of the coronary vasculature. However, the aim of this study was to correlate the local ESS pattern with plaque characteristics, and data from all the 3 major epicardial coronary arteries were included in the analysis. Third, all the patients enrolled in our study were admitted with ACS. Therefore, how our findings translate to other populations (e.g., patients with asymptomatic or stable disease) cannot be ascertained from our data and needs to be investigated in future studies. Fourth, because of the relatively shallow depth penetration of FD-OCT, quantification of plaque burden and remodeling, important predictors of plaque natural history, was not possible. Fifth, although we used an objective, validated approach, measurement of macrophage density as NSD of OCT signal within the fibrous cap might have been influenced by changes in the indices of refraction caused by adjacent plaque components, such as calcium or fibrous tissue. Therefore, our results need to be interpreted with caution and considered as hypothesis-generating. Sixth, although our study population included a large spectrum of atherosclerosis, from mild to moderate disease, segments with significant stenosis (>40% area stenosis) were excluded. This allowed us to minimize the effect of established and developing stenoses when assessing the preceding local hemodynamic behavior and to explore the relationship between baseline ESS and plaque features using OCT data at a single time point. Prospective studies with serial vascular profiling and imaging are warranted to further elucidate the cause–effect relationship between ESS and atherosclerosis. Finally, in flow modeling, we also acknowledge the assumption of Newtonian blood viscosity. However, it has been previously reported that this assumption does not create significant errors in the analysis and, more importantly, in the relative distribution of ESS values. Furthermore, blood viscosity had the same value for all cases irrespective of any differences in hematocrit among patients as previously implemented in ESS-related studies in humans.

Conclusions
Coronary regions exposed to low ESS are characterized by larger lipid burden, thinner fibrous cap, and higher prevalence of TCFA, underscoring the critical role of low ESS in the development of vulnerable plaques in humans. FD-OCT-based assessment of ESS and wall characteristics may be useful in identifying vulnerable coronary regions.

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Disclosures
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References

**CLINICAL PERSPECTIVE**

Atherosclerosis is characterized by focal and heterogeneous manifestations. Early identification of high-risk coronary regions likely to cause plaque rupture before the occurrence of adverse cardiac events would be of great clinical importance. This study represents the first in vivo evaluation of the relationship between local endothelial shear stress (ESS) and microscopic coronary plaque features in humans using computational fluid dynamics and frequency-domain optical coherence tomography analysis. In nonculprit arterial regions of patients presenting with acute coronary syndrome, we observed that areas with low local ESS were more frequently associated with the presence of thin-cap fibroatheroma, which is considered to be the prototype of the rupture-prone plaque. Additionally, plaques in areas with low ESS showed larger lipid accumulation, thinner fibrous cap, and greater macrophage density, which are established contributors to plaque vulnerability. Overall, the current findings potentiate the use of vascular profiling/ESS assessment for early detection of lesions prone to rupture and to precipitate in acute coronary syndromes. In the future, technology advancements might enable the accurate characterization of local ESS and plaque morphology using noninvasive approaches (i.e., MRI, multislice computed tomography), thus avoiding the small, yet existing, risk associated with invasive assessment of vascular characteristics. This may create opportunities for prophylactic and selective focal treatments, in addition to intensive systemic pharmacological therapies, which could potentially avert future adverse coronary events.
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